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10/633,204	07/30/2003	Shanta M. Modak	A33459-PCT-USA-A (070050.	3145
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EXAMINER CHOI, FRANK I				
ART UNIT		PAPER NUMBER		
1616				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary

Application No.

10/633,204

Applicant(s)

MODAK ET AL.

Examiner

FRANK I. CHOI

Art Unit

1616

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 August 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 7-16, 19-31, 33-37 and 39 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 7-16, 19-31, 33-37 and 39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/28/2008 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4,7-16, 19-31,33-37, 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raad et al. (US Pat. 5,688,516) in view of Domenico et al. (Journal of Antimicrobial Chemotherapy (1991)), WO 97/25085 and Darouiche et al. (US Pat. 6,719,991).

Raad et al. disclose that chelating agents, such as zinc citrate and citrate and bismuth, inhibit the formation of glycocalyx produced by staphylococci and Candida which glycocalyx helps said organisms adhere and stick to catheter surfaces (Column 1, lines 60-68, Column 2, lines 1-11, Column 4, lines 44,48,49,65,66). It is disclosed that a tetracycline antibiotic, such as minocycline which is effective in killing adherent staphylococci embedded in glycocalyx, is combined with said chelating agent and coated on the medical device (Column 6, lines 2-13, 40-50, claims 1,9,10,11,14-17). It is disclosed that the combination of tetracycline antibiotic and chelating agent can vary between about 0.001 to about 1,000 mg/ml, preferably between about 1

to about 200, or from 10 to about 100 mg/ml of the chelating agent (preferably between about 20 to about 100 or about 20 to about 60 mg/ml), and between about 0.001 to about 1000 mg/ml (preferable between about 10 to about 200 or from about 2 to about 100 mg/ml) and non-glycopeptide antimicrobial agent (preferably between about 10 to about 100, or about 2 to about 9 mg/ml) (Column 6, lines 56-68). It is disclosed that in addition to said concentration ranges, other concentration ranges for use in coating a medical device include between about 10 mg/ml and about 200 mg/ml of the non-glycopeptide antimicrobial agent, such as minocycline, and between 10mg/ml and about 200 mg/ml of the chelating agent with one embodiment including 60 mg/ml of each (Column 8, lines 8-23).

Domenic et al. disclose that effects on growth inhibition of bacteria is due to the bismuth ion, salicylate ions have an additive effect when combined with bismuth, and that bismuth subsalicylate is effective in inhibiting capsular polysaccharide production by bacteria which forms bacterial biofilm (Pages 801,808). It is disclosed that the activity of salicylate against bacteria is due in part to chelation of cations required by polysaccharide synthetic enzymes (Pg. 801).

WO 97/25085 disclose treating polymeric medical articles, such as vascular catheters, with 1-5 % chlorhexidine, such as chlorhexidine free base, diacetate, digluconate, 0.5-5% triclosan, and that silver sulfadiazine (.5-1 %) can also be included (Page 4, lines 13-15, Pages 5, 6, Page 7, lines 1-12). It is disclosed additional anti-infective agents such as benzalkonium chloride can also be added (page 14, lines 3-9). It is disclosed that in specific embodiments the impregnating solution comprises between 0.1 and 10% anti-infective agent (Page 13, lines 18-24).

Darouiche et al. ('991) disclose the combination of an antibiotic, such as minocycline, and antiseptic, such as chlorhexidine, triclosan or silver, for coating catheters (Column 4, lines 6-27, column 7, lines 8-36, Column 8, lines 16-35, Column 10, lines 4-21). An "effective concentration" is disclosed which is defined to mean that a sufficient amount of the antimicrobial agent is added to decrease, prevent or inhibit the growth of bacterial and/or fungal organisms; that will vary for each compound and upon known factors such as pharmaceutical characteristics, the type of medical device, use and length of use, etc.; and that it is within the skilled artisan's ability to relatively easily determine an effective concentration for each compound (Column 7, lines 49-57).

Raad et al. discloses the combination of chelating agents, such as zinc citrate and citrate and bismuth, with minocycline to prepare antimicrobial medical devices, such as catheters. The difference between the claimed invention and Raad et al. is that Raad et al. does not expressly disclose the combination of minocycline and chlorhexidine, the combination of minocycline, triclosan and bismuth, or minocycline and bismuth for treating a polymeric-containing medical articles. However, the prior art amply suggest the same as WO 97/25085 discloses that chlorhexidine, such as chlorhexidine digluconate, acetate or free base, can be combined with triclosan, silver sulfadiazine and benzalkonium chloride for preparing antimicrobial catheters; Domenic et al. disclose that bismuth ion inhibits bacterial growth, that bismuth subsalicylate is effective in inhibiting the formation of capsular polysaccharide by bacteria which forms bacterial biofilm, and that salicylate is a chelating agent; and Darouiche et al. ('991) disclose that minocycline can be combined with triclosan, chlorhexidine or silver for preparation of antimicrobial catheters.

“It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art.” *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie* obvious.). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held *prima facie* obvious). As such, it would have been well within the skill of one of ordinary skill in the art to modify the prior art as above with the expectation that the combination of minocycline and chlorhexidine, including gluconate, diacetate and/or free base, would be effective in preparing an antimicrobial catheter; and that the addition of bismuth, including bismuth salicylate or bismuth citrate, benzalkonium chloride, triclosan, silver and/or zinc would provided additional antimicrobial activity in the antimicrobial catheter.

Further, in view of the amount ranges disclosed above, the prior art discloses ranges of the above compounds that fall within, encompass or overlap the claimed ranges. In the case where the claimed ranges “overlap or lie inside ranges disclosed by the prior art” a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) (The prior art taught carbon

monoxide concentrations of “about 1-5%” while the claim was limited to “more than 5%.” The court held that “about 1-5%” allowed for concentrations slightly above 5% thus the ranges overlapped.); *In re Geisler*, 116 F.3d 1465, 1469-71, 43 USPQ2d 1362, 1365-66 (Fed. Cir. 1997) (Claim reciting thickness of a protective layer as falling within a range of “50 to 100 Angstroms” considered prima facie obvious in view of prior art reference teaching that “for suitable protection, the thickness of the protective layer should be not less than about 10 nm [i.e., 100 Angstroms].” The court stated that “by stating that suitable protection’ is provided if the protective layer is about’ 100 Angstroms thick, [the prior art reference] directly teaches the use of a thickness within [applicant’s] claimed range.”). Further, “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); See *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003)(“The normal desire of scientists or artisans to improve upon that is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.”).

The Examiner has duly considered the Applicant’s arguments but deems them unpersuasive.

The Applicant argues that the claimed combinations of active ingredients exhibit unexpected activity in that they have synergistic activity. However, it is not unexpected that the

combinations of compounds would act synergistically. See *Ex parte Quadranti*, 25 USP2d 1071, 1072 (Bd. Pat. App. & int. 1992) (in most case better than additive results could be expected).

Even if synergy was unexpected, the tested combinations were against specific species of microbes, use specific compounds and used specific amounts, whereas the claims are generally encompass any infective agent, claim ranges of amounts which are either wholly outside the tested amounts or are single data point within the claimed ranges. See *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (Evidence of the unobviousness of a broad range can be proven by a narrower range when one skilled in the art could ascertain a trend that would allow him to reasonably extend the probative value thereof.). Since there was little or no variance as to the amounts of each compound in the allegedly synergistic compositions in over the different tests where amounts were used that fell within the claimed ranges, it does not appear that a trend could be ascertained as to whether synergism would be present over the entire claimed ranges. Further, with respect to claim 39, the data does not show any synergistic activity with respect to the combination of minocycline and bismuth salt (Remarks (8/28/2008), page 9 (combination of minocycline and bismuth nitrate was similar to benzalkonium chloride alone)). As such, the data cited is not commensurate in scope with the claims.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

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is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4,7-16, 19-31,33-37, 39 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-55 of US Pat. 6,106,505 in view of Raad et al. (US Pat. 5,688,516), Domenico et al. (Journal of Antimicrobial Chemotherapy (1991)), WO 97/25085 and Darouiche et al. (US Pat. 6,719,991).

Claims 1-55 of US Pat. 6,106,505 claim an anti-infective medical articles, such as an intravenous catheter, which have been impregnated with a solution containing the combination of 1-5% chlorhexidine free base and 0.5-5% triclosan, which can further contain silver sulfadiazine (See claims 1-55).

Raad et al. (US Pat. 5,688,516), Domenico et al. (Journal of Antimicrobial Chemotherapy (1991)), WO 97/25085 and Darouiche et al. (US Pat. 6,719,991) are cited for the same reasons as above and are incorporated herein to avoid repetition.

US Pat. 6,106,505 claims anti-infective medical articles, such as intravascular catheters, which contain the combination of chlorhexidine and triclosan, which can further contain silver sulfadiazine. The difference between the claimed invention and the claims of US Pat 6,106,505

is that said US Patent does not expressly claim the combination of minocycline and chlorhexidine, the combination of minocycline, triclosan and bismuth, or the combination of minocycline and bismuth for coating medical devices, such as intravascular catheters. However, the prior art amply suggests the same as indicated above. As such, it would have been well within the skill of one of ordinary skill in the art to modify the claims of the '505 patent prior art as above with the expectation that the addition of minocycline or minocycline and bismuth, including bismuth salicylate or bismuth citrate, would increase the antimicrobial activity of the antimicrobial medical device. Examiner recognizes that independent claim 39 of the present application does not recite either the use of chlorhexidine or triclosan. However, since it would be obvious to add minocycline and bismuth to claims of the '505 patent, said modification of the claims of the '505 patent would read on claim 39 of the present application. Further, it would have been well within the skill of one of ordinary skill in the art to use chlorhexidine gluconate, chlorhexidine free base and/or chlorhexidine diacetate in the claims of the '505 patent with the expectation that the same would be effective antiseptic agents for use in the medical devices and to add benzalkonium chloride or zinc citrate with the expectation that the same would increase the antimicrobial activity of the antimicrobial medical devices. Further, as indicated above, in view of the teachings of the prior art and the claims of the '505 patent, the claimed concentration ranges are *prima facie* obvious.

Therefore, the claimed invention, as a whole, would have been an obvious modification of the claims of US Pat. 6,106,505 to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of said claims and references.

The Examiner acknowledges the Applicant's statement that a terminal disclaimer will not be filed as to the '505 patent until allowable subject matter is indicated. As such, the obviousness double patenting rejection of claims 1-4,7-16, 19-31,33-37, 39 over the claims of the '505 patent in view of the prior art is maintained

Claims 1-4,7-16, 19-31, 33-37, 39 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of US Pat. 6,582,719 in view of Raad et al. (US Pat. 5,688,516), Domenico et al. (Journal of Antimicrobial Chemotherapy (1991)) and WO 97/25085.

Claims 1-15 of US Pat. 6,582,719 claim an anti-infective medical article prepared by exposing a polymer-containing medical article with a solution containing 1-8% minocycline and 1-8% chlorhexidine free base or chlorhexidine diacetate, which can further contain 0.5-2% bismuth nitrate and/or 0.2-1.0% benzalkonium chloride; a solution containing said minocycline, 1-8% triclosan and said bismuth nitrate, which can further contain said benzalkonium chloride; a solution containing said minocycline and said bismuth nitrate; and intravascular catheters containing the combination of minocycline and chlorhexidine free base or chlorhexidine diacetate, which can further contain bismuth nitrate, benzalkonium chloride, silver sulfadiazine or silver carbonate; or the combination of minocycline, triclosan and bismuth nitrate, which can further contain benzalkonium chloride or silver carbonate (See claims 1-15).

Raad et al. (US Pat. 5,688,516), Domenico et al. (Journal of Antimicrobial Chemotherapy (1991)) and WO 97/25085 are cited for the same reasons as above and are incorporated herein to avoid repetition.

US Pat. 6,582,719 claims anti-infective medical articles, such as intravascular catheters, which contains the combination of minocycline and chlorhexidine; the combination of minocycline, triclosan and bismuth; and the combination of minocycline and bismuth. The difference between the claimed invention and the claims of US Pat 6,582,719 is that said US Patent does not expressly claim the use of bismuth citrate or bismuth salicylate, chlorhexidine gluconate or zinc salt. However, the prior art suggests the same as indicated above. As such, it would have been well within the skill of one of ordinary skill in the art to modify the claims of the '719 to use bismuth citrate or bismuth salicylate in place of or in addition to bismuth nitrate with the expectation that the chelating activity of the salicylate or citrate would provide increased antibacterial activity, that zinc citrate would increase the antimicrobial activity of the antimicrobial medical device, and that to use chlorhexidine gluconate, chlorhexidine free base and/or chlorhexidine diacetate with the expectation that the same would effective antiseptic agents for use in the medical devices. Further, as indicated above, in view of the teachings of the prior art and the claims of the '719, the claimed concentration ranges are *prima facie* obvious.

Therefore, the claimed invention, as a whole, would have been an obvious modification of the claims of US Pat. 6,582,719 to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of said claims and references.

The Examiner acknowledges the Applicant's statement that a terminal disclaimer will not be filed as to the '719 patent until allowable subject matter is indicated. As such, the obviousness double patenting rejection of claims 1-4, 7-16, 19-31, 33-37, 39 over the claims of the '719 patent in view of the prior art is maintained.

Conclusion

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (571)272-0610. Examiner maintains a compressed schedule and may be reached Monday, Tuesday, Thursday, Friday, 6:00 am – 4:30 pm (EST).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Johann R. Richter, can be reached at (571)272-0646. Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Frank Choi
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October 7, 2008

/Johann R. Richter/
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